Massive transfusion in trauma

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Purpose of review
The purpose of this review is to provide an overview of currently recommended treatment approaches for traumatic hemorrhage shock, with a special focus on massive transfusion.

Recent findings
Severe trauma patients require massive transfusion, but consensual international definitions for traumatic hemorrhage shock and massive transfusion are missing. Current literature defines a massive transfusion as transfusion of a minimum of 3–4 packed red blood cells within 1 h. Using standard laboratory and/or viscoelastic tests, earliest diagnosis and treatment should focus on trauma-induced coagulopathy and substitution of substantiated deficiencies.

Summary
To initiate therapy immediately massive transfusion protocols are helpful focusing on early hemorrhage control using hemostatic dressing and tourniquets, correction of metabolic derangements to decrease coagulopathy and substitution according to viscoelastic assays and blood gases analysis with tranexamic acid, fibrinogen concentrate, red blood cells, plasma and platelets are recommended. Alternatively, the use of whole blood is possible. If needed, further support using prothrombin complex, factor XIII or desmopressin is suggested.

Keywords
blood component, hemorrhage, massive transfusion, traumatic injury, viscoelastic hemostatic assay

INTRODUCTION

Trauma accounts for 15% of perioperative massive transfusion (MT) [1▪▪,2▪▪] and, following traumatic brain injury (TBI), hemorrhage remains the leading cause of death, especially in individuals aged ≤46 years [3▪]. Hemorrhagic shock (HS) is present in up to 40%; nevertheless, in 12–34% of trauma and hemorrhage, deaths are preventable [4▪]. Some 6 percentage of trauma patients appear to be at risk of requiring MT [1▪▪,5▪]. This review will focus on recent developments in MT in trauma.

METHODS

We performed a selective review of the literature using structured search strategies in a timeframe from 2003 to 2023.

DEFINITION

MT is a treatment for massive hemorrhage. The European guideline on management of severe perioperative bleeding defines 'severe' as beyond 20% of total blood volume [TBV) [6▪▪]. Both class III [30–40% loss of TBV, systolic blood pressure (SBP) <90 mmHg, heart rate ([HR) ≥120/min and thready] and class IV (>40% TBV) of the Advanced Trauma Life Support's four classes of hemorrhage should be considered as 'massive' [1▪▪,7▪]. Blood loss (BL) of 1.5 l, which equals approximately 30% of an adult's TBV, causes consistent hypotension [4▪]. A consensual international definition of traumatic HS is necessary but missing: the most used parameters are Shock Index (SI; ≥0.9), SBP, base excess (BE; ≤−5 mmol/l), lactate (>3 mmol/l), and number of transfused packed red blood cells (pRBC) [8▪▪]. Using SI, defined as HR divided by SBP, a systematic review including a total of 670 728 trauma patients showed values correlated with the degree of shock and impaired tissue perfusion, SI >1 is indicative of

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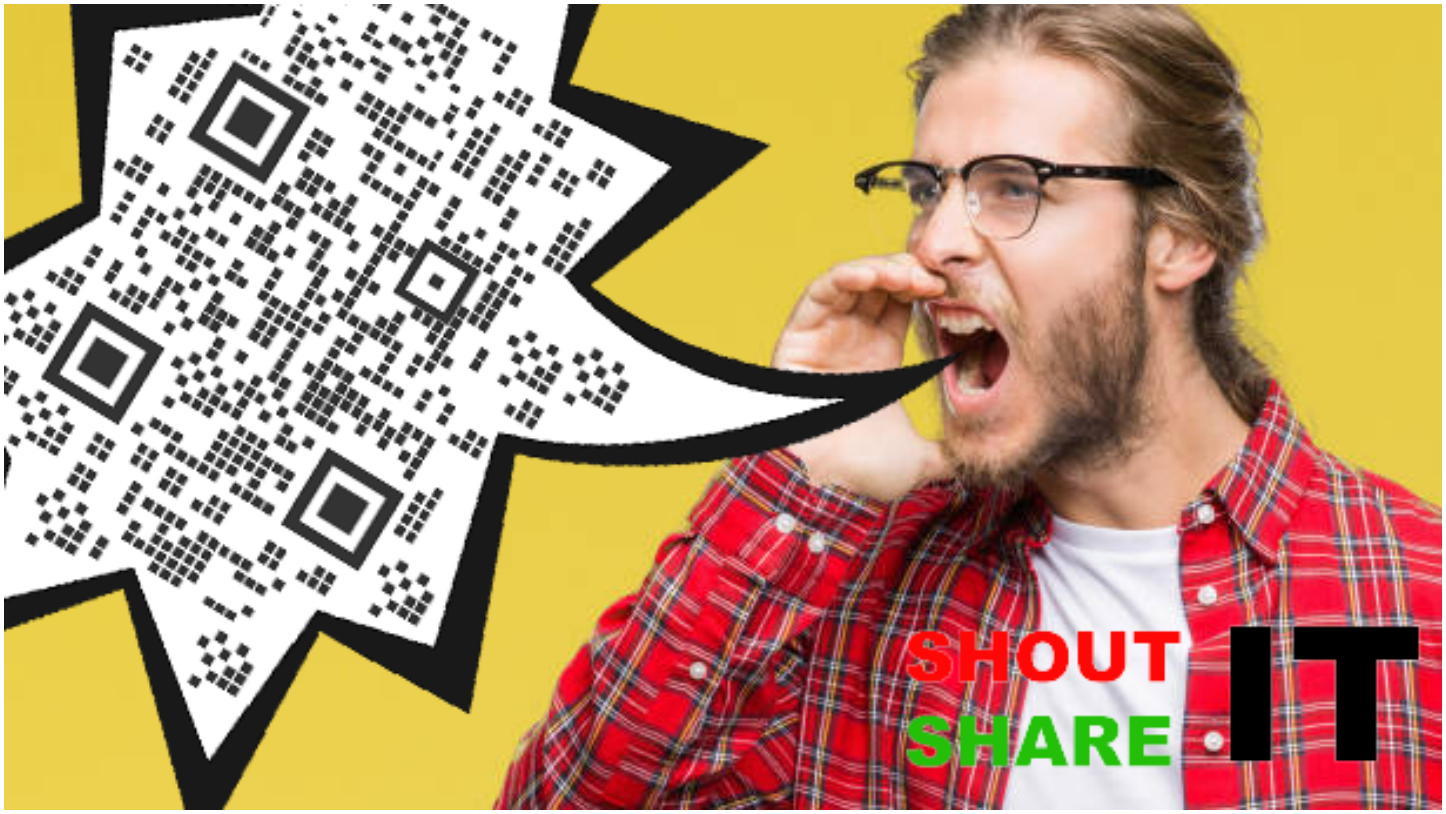
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KEY POINTS

- Continuous measurement of temperature and serial measurement of blood gases.
- Initially ratio-driven, as soon as possible concentrate based individualized goal-directed substitution.
- For HS: permissive hypotension; 15 mg/kg tranexamic acid; fibrinogen aiming at 2.2–2.5 g/l; PCC 25 IU/kg; factor XIII (if <60%) 20 IU/kg.
- Consider cell salvage.

suspect HS, but should not be used as a sole parameter [9▪▪]. The British 2022 Guideline on major hemorrhage abstained from a definition, but emphasized the patient's clinical status (e.g., HR > 110/min and/or SBP < 90 mmHg). An increased risk of massive hemorrhage is to be expected in adults with SBP <70 mmHg, adults with HR >110/min and SBP <90 mmHg (the most recurrent definition for HS [8▪▪]), penetrating injury or major fractures, and fluid in body cavities likely to be blood [1▪▪]. Most definitions use the transfused number of pRBC. Multiple definitions for MT are published, varying greatly in cut-offs for volume transfused and time frame [2▪▪]. MT's historical definition dates to the Vietnam War and entails ≥10RBC/24 h [5▪]. As most exsanguinating deaths occur within 2 h of bleeding onset [4▪], using 24 h will imply a 'survivorship bias' [2▪▪,8▪▪]. MT is an outcome measure encompassing both patients' wellbeing and resource utilization [2▪▪]. Table 1 lists possible definitions for MT.

Table 1. Definitions of MT

Traditional definition	≥10 pRBC/24 h ≥20 pRBC/24 h (ultra massive)
Modern definition	≥10 pRBC/6 h ≥20 pRBC/4 h (ultra massive) ≥4pRBC/1 h Loss of ≥50% TBV/3 h Loss of TBV in 24 h
Substantial bleeding	≥1 pRBC within 2 h and ≥5 pRBC or bleeding-related death within 4 h
Resuscitation intensity (RI)	Number of units infused within 30 min of arrival 1 unit = 1 l crystalline solution, 0.5 l colloid, 1 pRBC, 1 plasma, or 6 platelets (~ 1 pooled or apheresis unit)
Critical administration threshold (CAT) positive	≥3 pRBC CAT24 h: in any 1 h within 24 h of arrival CAT1 h: within 1 h CAT4 h: in any 1 h within 4 h

Compared to ≥10RBC/24 h, 'CAT positive' has the best sensitivity, but 'RI positive' has better specificity as well as better positive and negative predictive values [1▪▪]. RI is the only definition not exclusively using pRBC [2▪▪]. pRBC, packed red blood cells, TBV, total blood volume.

PATHOPHYSIOLOGY

Impaired microcirculation leads to cellular hypoxia causing endothelial damage. Loss of the endothelial glycocalyx is emerging as a unifying mechanism linking the endotheliopathy of trauma with microvascular inflammation, barrier leakage, coagulopathy, and organ injury. Endothelial injury and glycocalyx shedding, causing sympathoadrenal activation, occurring 5–8 min after injury and persisting for 24 h, are determined by the severity of HS. Both hypoxia and hypoperfusion cause release of tissue-plasminogen activator (t-PA) from endothelial Weibel-Palade bodies. Rather than the injury itself, downstream effects of the injury are postulated to result in glycocalyx degradation causing hyperfibrinolysis and increased mortality. Microcirculatory derangements can persist despite adequate macrocirculation corrected by vasopressors or transfusion. This ischemia-induced hyperfibrinolysis is a major contributor to trauma-induced coagulopathy (TIC) and of special importance in low-flow states [10▪,11▪,12▪▪,13▪].

DIAGNOSTICS

Coagulopathy might visually be diagnosed by non-surgical, diffuse bleeding from mucosa, serosa, wounds as well as punction sites of intravascular catheters. Basic analysis requires early and repetitive measurements of blood gases (BGA), blood typing, and conventional coagulation tests (CCT), that is, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, platelet count [6▪▪,14▪▪,15▪▪].

Early and serial BGAs and temperature are the easiest, cheapest, and fastest monitoring and should be done every 20–30 min or every 4 pRBC in patients being actively resuscitated [1▪▪,15▪▪,16▪▪]. Increasing lactate and negative BE are sensitive tests to monitor the extent of bleeding and tissue hypoperfusion, essential for diagnosing coagulopathy [15▪▪–17▪▪], and indicative even prehospitally [18▪]. The context of hypothermia, acidosis and coagulopathy is emphasized by the terms "*bloody vicious cycle*" [19], "*lethal triad*" [20], and "*triad of death*" [21]. A recent focus on transfusion- and trauma-induced hypocalcemia as a fourth inducing coagulopathy aimed at an ionized calcium of

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>0.9 mmol/l [6▪▪] and introduced the term *"death diamond"* [22]. Figure 1 lists these parameters.

It is well recognized that CCT may not provide real-time assessment of a patient's hemostatic status, a more rapid generation of results will improve patient care [1▪▪]. Additionally, PT and aPTT were not designed to monitor coagulation deficiencies during hemorrhage. Use of point-of-care devices in MT is effective for both, diagnostics and therapy: viscoelastic hemostatic assays (VHA) and platelet *function* analyzers. VHA are highly specific for hyperfibrinolysis, more sensitive in the early detection of coagulopathy than CCT, might improve survival [6▪▪,23▪] and are useful to guide individualized goal-directed coagulation therapy [6▪▪,15▪▪–17▪▪]. Regardless of BL, VHA's high negative predictive value indicates when there is no need for supplementation thereby reducing unnecessary transfusion! The German 2023 guideline uses a grade of recommendation A for VHA and B for platelet function [14▪▪]; the European guideline states, that diagnostic cut-offs for pathologic platelet dysfunction after traumatic injury have not been established [17▪▪].

THERAPY

The main approach must be to prevent MT [4▪,5▪,6▪▪]. Therefore, a stepwise concept of direct pressure, hemostatic-impregnated compression dressings and tourniquets should be used initially to control bleeding [14▪▪,15▪▪].

With signs of ongoing bleeding, hemodynamic instability or clinical gestalt, therapy should rapidly be started [24▪].

Synthetic colloids should be avoided [16▪▪]. Contemporary strategies minimize balanced crystalloid use ("restrictive volume replacement strategy") [16▪▪,25▪].

MASSIVE TRANSFUSION PROTOCOL

Local establishment of site-specific, standardized, multidisciplinary massive transfusion protocols (MTP) with predefined cut-offs, components, and ratios form the basis of standardizing transfusion [6▪▪,15▪▪,16▪▪,26▪▪].

WARMING DEVICES

Exclusively warmed fluids and the use of warming devices are essential for fluid therapy [15▪▪,26▪▪].

DAMAGE CONTROL RESUSCITATION

Damage control resuscitation (DCR) focuses on the early use of whole blood (WB) or blood product ratios, early hemorrhage control, permissive hypotension to promote hemostasis, and correction of ongoing metabolic derangements, followed by rapid definitive hemorrhage control [24▪].

RED BLOOD CELLS

The decision to transfuse is always an individual one [27▪]. RBC are used to maintain hemoglobin (Hb) at a level high enough to support adequate oxygen delivery to the tissues. Transfusion is usually required when 30–40% of TBV is lost (~1500 ml in a 70 kg male). Loss of more than 40% TBV

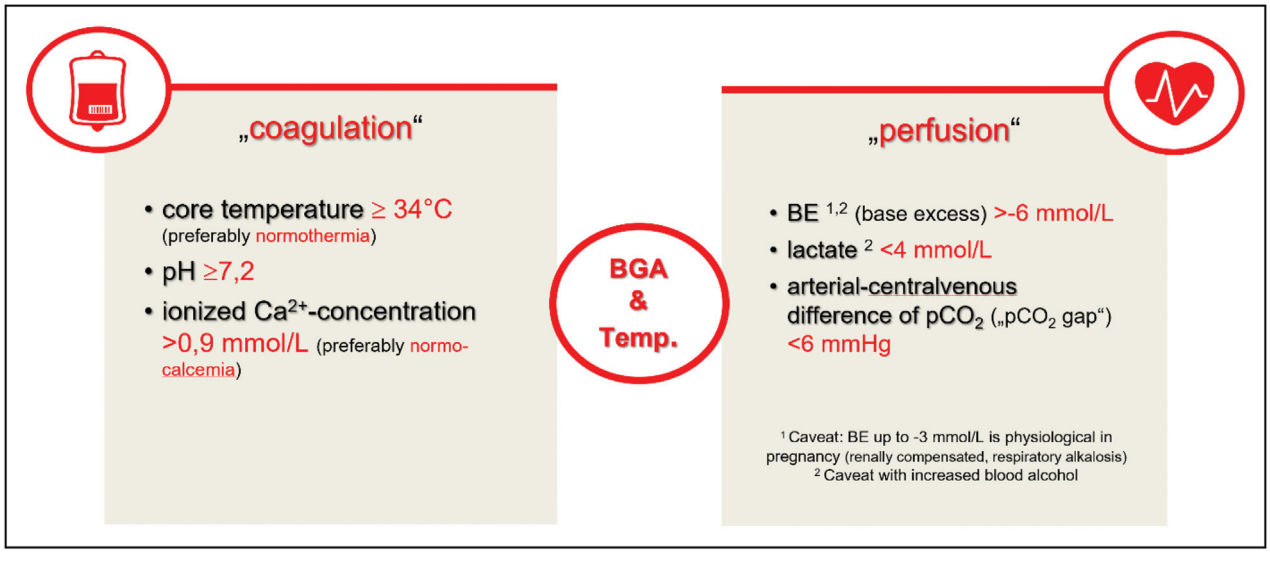
„coagulation"
• core temperature ≥ 34°C (preferably normothermia)
• pH ≥7,2
• ionized Ca2+-concentration >0,9 mmol/L (preferably normocalcemia)
BGA & Temp.
„perfusion"
• BE 1,2 (base excess) >-6 mmol/L
• lactate 2 <4 mmol/L
• arterial-centralvenous difference of pCO2 („pCO2 gap") <6 mmHg
1 Caveat: BE up to -3 mmol/L is physiological in pregnancy (renally compensated, respiratory alkalosis)
2 Caveat with increased blood alcohol

FIGURE 1. Preconditions for functional hemostasis. Treatment targets are given for resuscitation of coagulation and perfusion (modified with a CC-BY-NC-license by Karger).

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(1500–2000 ml) is life threatening and requires immediate transfusion [16▪▪,26▪▪]. A restrictive transfusion threshold of 70–90 g/l (4.3–5.6 mmol/l) was proven to be, at least, noninferior for trauma [28]. Especially in MT, Hb concentration may remain falsely elevated despite significant BL due to inadequate fluid resuscitation. After bleeding control, there is no indication to aim at physiological Hb-levels [26▪▪].

Blood type O, the most common blood type, has lower von Willebrand factor (vWF) and FVIII levels (25–35% lower than non-O blood types); this might be associated with increased bleeding, hyperfibrinolysis, and MT post injury [29].

RBC transfusion should be ABO-identically. Emergency transfusion of un-crossed blood group O is only indicated for vital risk [27▪]. The risk of D-alloimmunization following RhD-positive transfusion seems to be smaller than previously thought [30].

PLASMA

Most plasma consists of either fresh frozen, single-donor plasma (FFP) or pooled plasma from a certain number of donors, for example, solvent/detergent (SD-) treated plasma [31▪▪]. Single-donor plasma contains a variable activity of individual coagulation factors (especially FI and FVIII). FFP is standardized on a FVIII-activity of 70% following thawing. Pathogen-reduction or virus-inactivation by different chemical additives causes additional reduction of specific factors.

FFP should be group-identical to the patient. Group A plasma is now also available for untyped patients demonstrating noninferiority to AB-plasma, the impact of plasma ABO-incompatibility on clinical outcomes is insignificant [25▪]. Being a superior isometric buffer compared to crystalloids, plasma is an ideal volume expander in the intravascular space, has a homeostatic effect on endothelial function and innate immune system activation [25▪,32]. FFP-based resuscitation improves intestinal perfusion immediately following resuscitation, which correlates with improved tissue oxygenation and decreased tissue CO_2-levels [33]. A clinical and significant increase of coagulation factor activities can be achieved by large volumes of plasma only (>30 ml/kg) [31▪▪]. Therefore, the main indication of plasma might be MT [27▪].

PLATELET CONCENTRATES

Due to a lack of controlled trials, an evidence-based statement on platelet cut-offs in different clinical settings is not possible. Based on expert opinion, most guidelines recommend platelet concentrate (PC) for MT if platelet count is <75–100 G/L or a loss of 1.5× TBV [15▪▪,16▪▪,26▪▪,27▪]. Platelet count and platelet function do not necessarily correlate [27▪]. Both quantitative and qualitative platelet damages are more marked when tissue injury is severe, transfusion is large, and hypoperfusion is intense and prolonged. Variations of platelet count within 'normal ranges' might reflect trauma severity and coagulopathy; early platelet transfusion despite normal platelet count might be beneficial [34▪]. Beside PC, the clot's firmness can be increased by desmopressin and/or blocking of fibrinolysis by tranexamic acid (TXA) [6▪▪,26▪▪,27▪].

RATIO

Ratio describes the unit ratios of RBC to FFP to PC. Of note, the order of the components is not standardized. Additionally, different formulations of PC might cause a mix-up of these numbers: One apheresis unit is equivalent to 5-6 whole blood (WB)-derived units. The pooled units available in Australia, Canada and Europe have lower numbers of platelets equivalent to 4–5 single donors. Using pathogen-reduction will cause significant reduction in platelet recovery [1▪▪].

The PROPPR-trial remains the only prospective RCT to find reduced mortality by a 1 : 1:1 ratio; but only for 3 h-mortality, not for 24 h or 30d [35]. This was only achieved when components were available within 8 min of calling the blood bank and artificial colloid fluid use was markedly restricted [36]. A post hoc analysis using Bayesian hierarchical models indicated "strong" to "decisive" supporting evidence in favor of balanced transfusions [37]. Almost all international guidelines recommend this ratio as initial therapy in MT: RBC and plasma initially in a 1 : 1 ratio (not less than 2 : 1) [16▪▪,17▪▪,26▪▪]; RBC:FFP:PC in a 1 : 1:1 (using US PC) [25▪] or 4 : 4:1 ratio (using Australian or German pooled or apheresis PC) [14▪▪,15▪▪], respectively; and a high PC:RBC ratio [17▪▪]. Using the Trauma Quality Improvement Program database, for patients receiving >10 pRBC, increasing RBC:PC and RBC:FFP ratios were consistently associated with increased odds of 4h-mortality [38▪].

In MT, a 'hybrid approach' shall be used: beginning with 'ratio-driven', resuscitation measures shall as soon as possible be continued using an individualized goal-directed strategy, guided by VHA and/or CCT [6▪▪,14▪▪–17▪▪,26▪▪,27▪].

WHOLE BLOOD

The manufacturing process of separating donated blood into single components necessitates the

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addition of ~25% of each bag's volume in additives, preservatives, and stabilizers. Therefore, 1RBC + 1FFP + 1PC will not have the same coagulation activity as the same volume of WB. Recent prospective trials of WB in the civilian setting found increased survival: A prospective observational cohort study of 1377 trauma patients requiring un-crossmatched products found a fourfold increased survival and 60% reduction in overall transfusions [39▪▪]. A 14-center, prospective observational study showed 1623 WB patients to be 9% less likely to experience bleeding complications and 48% less likely to die [40▪]. A prospective, multicenter, observational cohort study of 7 trauma centers with 1051 patients noted in patients with an elevated prehospital probability of mortality a 48% lower risk of 4h-mortality and a 30% lower risk of 28d-mortality [41▪]. A meta-analysis of 20 studies up to January 2023 confirmed lower early and 24h-mortality in WB groups [42▪▪]. A recent meta-analysis showed transfusion with WB + components is associated with lower 24-h mortality vs. component alone and transfusion with WB is associated with a lower volume of RBC transfused at both 6 and 24 h [43▪]. On average, these results were reached with 2 units of WB combined with components. In the USA, low titer type O whole blood (LTOWB), a FDA cleared WB product, is increasingly used for massively bleeding civilians [24▪].

TRANEXAMIC ACID

As hypoxia and hypoperfusion are common in HS and MT and main triggers of hyperfibrinolysis, the early use of TXA is indicated; the administration of TXA shall not await results from VHA [6▪▪,17▪▪]. The recommended dose is 15 mg/kg or 1 g for an adult. Routine administration of a second dose might not be indicated, only in case of persistent or recurrent hyperfibrinolysis [44▪].

COAGULATION FACTOR CONCENTRATES

In the early treatment phase of uncontrolled massive bleeding, a MT with a high ratio (≥1 : 1) of plasma to RBCs is suggested; but, as soon as possible, a concentrate based individualized targeted controlled coagulation management is recommended [6▪▪].

FIBRINOGEN

Hypofibrinogenemia is common in MT. Trauma patients undergoing MT with decreased admission fibrinogen (<2 g/l) demonstrate increased mortality [23▪]. Fibrinogen's physiological concentration of 2.5 g/L is associated with enhanced endothelial barrier integrity [45]. FFP is impractical for increasing fibrinogen levels >1.5 g/l, and supplementation in the form of cryoprecipitate or fibrinogen concentrate (FC) should be chosen [6▪▪,16▪▪,17▪▪,26▪▪,27▪]. Compared to FC, cryoprecipitate appears considerably less predictable for bleeding management due to wide variation in pro- and anticoagulation factors, the presence of PMPs, and the potential to elevate VWF and FVIII to prothrombotic levels [46]. The German guideline recommends FC for life-threatening bleeding and/or HS [14▪▪]. Substitution is indicated, if plasma concentration is <1.5–2 g/l [6▪▪,16▪▪,17▪▪,26▪▪,27▪,47] and should aim at 2.2–2.5 g/l [14▪▪,48,49] or respective VHA-results. An initial dose might be 3–6 g in an adult [15▪▪,16▪▪,26▪▪] or 30–60 mg/kg [14▪▪,16▪▪]. A postulated risk for thromboembolism following FC was never substantiated, probably because of a negative feedback-mechanism of FI as an acute-phase-protein.

PROTHROMBIN COMPLEX CONCENTRATES

Initially, thrombin generation is not impaired in trauma; however, it is substantially depressed by increasing shock with hypoperfusion [50]. Stimulation of thrombin generation might be induced by 4-factor prothrombin complex concentrates (PCC). In the massively bleeding patient with coagulopathy, the administration of an initial bolus of 25 IU/kg is recommended, in those with a high risk for thromboembolic complications an initial half-dose bolus (12.5 IU/kg) should be considered [51]. In a meta-analysis and compared with FFP only, PCC + FFP demonstrated better survival rate, favorable clinical recovery and no elevation of thromboembolism events [52]. Among 2238 adults treated for reversal of warfarin-associated bleeding, receipt of ~25 IU/kg 4F-PCC was not associated with an excess risk of thromboembolic events at 45 days compared with plasma therapy [53▪]. However, in 324 trauma patients with a median injury severity score (ISS) of 36 (26–50) receiving ≥1 pRBC and 25 IU/kg of PCC, thromboembolic events were more common (35% vs. 24%) [54▪]. In this PROCOAG-trial, 40% of patients received ≥3 RBC within the first hour, a median of 6 (4–10) RBC and had a trend towards better survival (+2% for 24 h and 28 days); the endpoint was confounded by survival bias and the product used may differ in efficacy from other PCC [24▪,55]. The German guideline recommends PCC for life-threatening bleeding and/or HS [14▪▪] and only, if fibrinogen is adequate [6▪▪,14▪▪,17▪▪]. Following PCC,

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a thromboembolic rate of 4–11% is recorded and a thorough benefit-risk assessment recommended [27▪,56].

FACTOR XIII

Supported by calcium, FXIII is responsible for covalent fibrin stabilization. With increased BL and hyperfibrinolysis, an acquired FXIII-deficiency is not a rare event [6▪▪,27▪]. FXIII should be monitored in bleeding patients and, in case of functional deficiency, supplemented [17▪▪]. The use of FXIII concentrate with 20 IU/kg at a FXIII level <60% is recommended in some guidelines [14▪▪,17▪▪], albeit this cut-off is still in discussion [6▪▪].

DESMOPRESSIN

In acquired von Willebrand syndrome, that is, platelet function impaired by hypothermia, acidemia, some diseases (valvular, myeloproliferative), extracorporeal assist devices, or drugs (ASS, COX1-inhibitors, ...), weak evidence indicates application of desmopressin (0.3 mg/kg as short infusion) [6▪▪,16▪▪,27▪].

CELL SALVAGE

For every BL >10% TBV, the use of intraoperative cell salvage shall be considered. A more liberal indication for re-transfusion of salvaged blood (compared to RBC) is justified by reduced risks [27▪]. If surgery for malignancy is still a contraindication remains debatable [57].

PERMISSIVE HYPOTENSION

The latest meta-analysis showed significant in-hospital and 30-day survival benefit by permissive hypotension; yet the optimal blood pressure for the individual patient remains vague [58,59]. This is shown by different targets in different guidelines: mean arterial pressure (MAP) 65 mmHg [14▪▪] vs. 50–60 mmHg [16▪▪,17▪▪] or, for traumatic brain injury (TBI), ~85 mmHg [14▪▪] vs. ≥80 mmHg [17▪▪]. The currently available data should be interpreted with caution [17▪▪]. The extent and treatment of HS must be monitored by serial measurement of lactate and BE [14▪▪]. Of note, permissive hypotension should be a temporary measure until the cause of bleeding has been controlled [16▪▪]. If the strategy of restricted volume replacement and permissive hypotension fails to achieve the target blood pressure, transient noradrenaline and/or vasopressin is recommended to maintain tissue perfusion [16▪▪,17▪▪,60].

PEDIATRIC TRAUMATIC HEMORRHAGIC SHOCK

There is little high-quality evidence available to guide specific aspects of hemorrhage control and specific resuscitation practices in this population. In children unlike adults, blood pressure alone is an insensitive indicator of hemorrhagic shock. DCR's principles are largely the same in pediatric and adult patients [61▪]. Recently, the recommendations of a consensus conference were published suggesting comparable but weight-adapted options [62▪▪]. Blood products should be prioritized over crystalloid for pre and in-hospital resuscitation.

MISCELLANEOUS

Morbidity and mortality rates increase as transfusion requirements increase [2▪▪]; yet, there is a debate whether the absolute transfusion volume or the transfusion rate (i.e., >7 units/h at 24 h) provides better discriminatory power for mortality [3▪]. Based on high transfusion volumes alone, futility of resuscitation should not be declared in MT [63]; constantly reevaluating the need for ongoing transfusion is recommended [3▪]. However, during a time of urgent blood bank shortage, a combination of the recently proposed evidence-based STOP-criteria [64] and certain VHA results [65] might be helpful in this evaluation.

Following MT (≥5 RBC within 4 h) about 7% of the patients form new alloantibodies; an independent association with new alloantibody formation was found for transfusion of D-positive RBC to D-negative patients and, to a lesser extent, D-positive PC to D-negative patients, and ≥11RBC in 24 h [66].

PROPHYLAXIS OF THROMBOSIS

Within 24 h following stop of bleeding, start and type of thrombosis prophylaxis should be determined [6▪▪,27▪].

CONCLUSION

HS and MT remain challenging tasks for our multidisciplinary teams. The availability of standardized MTP with predefined cut-offs is essential for being prepared. Serial laboratory measurements are essential and VHA very helpful. The ratio-driven therapy should soon be followed by a goal-directed one.

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Conflicts of interest

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B.H.: lecture fees from CSL Behring.

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